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ELMORE CRAIG, P.C.
209 MAIN STREET
N. CHELMSFORD, MA 01863

EXAMINER	
HAGHIGHATIAN, MINA	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/822,716
Filing Date: March 30, 2001
Appellant(s): EDWARDS ET AL.

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/27/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement of the grouping of the claims in the brief is correct

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6,043,214	Jensen et al	03-2000
6,284,282	Maa et al	09-2001
6,309,623	Weers et al	10-2001

International Ingredient Dictionary and Handbook.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-10, 12-17, 21-26, 28, 49 and 51-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (6,043,214) in view of Maa et al (6,284,282 B1).

Jensen et al teach method for producing powder formulation comprising an insulin. Jensen discloses that administration of insulin via the pulmonary route can be accomplished by either an aqueous solution or a powder preparation. Regarding the stability of proteins, Jensen discloses that so far all powder formulations have been described as mainly amorphous. It has been found that when insulin is combined with as appropriate absorption enhancer and is introduced into the lower respiratory tract in the form of a powder of appropriate particle size, it readily enters the systemic circulation by absorption through the layer of epithelial cells in the lower respiratory tract (col. 1, lines 51-67).

Jensen et al teach a dry powder composition comprising insulin or an analogue or derivative thereof, an enhancer and zinc (col. 2, lines 40-64). Jensen discloses that the enhancer can be a phospholipid such as lysophosphatidylcholine (col. 3, lines 1-8).

The compositions of Jensen generally are said to include between 2 and 12 Zn atoms per insulin hexamer (col. 3, lines 40-48). Examples I, III and IV include a 4% Zinc chloride solution. Jensen also discloses that the preferred analogues of insulin are the ones that include amino acids such as alanine, leucine, valine, etc (col. 2, lines 23-27; col. 3, lines 13-17). Jensen et al teach that the size of the particles is between 1 and 5

microns (col. 4, line 46-47). The formulations of Jensen are said to optionally include a carrier or excipient generally accepted for pulmonary administration (col. 4, lines 9-14). Jensen et al lacks specific disclosure on tap density of the powder particles.

Maa et al discloses a method of spray freeze drying proteins for pharmaceutical administration. The said dry powder compositions comprising particles of a protein of a mean diameter of less than 5 micron (col. 2, lines 10-20). The protein particles are also said to have a tap density of less than about 0.8 g/cm^3, with a tap density of less than about 0.4 g/cm^3 being preferred and less than about 0.1 g/cm^3 being especially preferred (col. 6, lines 5-12). Maa et al discloses proteins which include insulin (col. 6, line 46).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of a powder formulation of insulin of Jensen et al, to have looked in the art for specific particle characteristics such as tap density, as disclosed by Maa et al, with the reasonable expectations of preparing effective formulations for pulmonary delivery by improving their dispersibility, absorbability and respirability.

Claims 1-17, 21-28, 30-40, 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (6,043,214) in view of Weers et al (6,309,623 B1).

Jensen et al, discussed above, lacks specific disclosure on tap density and geometric diameter of the insulin particles.

Weers et al teach stabilized preparations for the delivery of a bioactive agent to the respiratory tract of a patient using a metered dose inhaler. The particles are said to have a mean geometric diameter of less than 20 micrometer or less than 10 micrometer, and most preferably less than about 5 micrometer (col. 13, lines 34-45).

Weers teaches the particles to have a tap density of less than 0.5 g/cm^3 and most often less than about 0.1 g/cm^3 (col. 14, lines 28-31). The mean aerodynamic diameter of the particles is less than about 3 micrometer. Said particle distributions will act to increase the deep lung deposition of the administered agent (col. 14, lines 38-43). Weers also discloses that the said inhalation formulations contain active agents such as proteins and peptide including insulin (col. 19, lines 50-54; col. 20, line 6).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of a powder formulation of insulin of Jensen et al, to have looked in the art for specific particle characteristics such as tap density, as disclosed by Maa et al, with the reasonable expectations of preparing effective formulations for pulmonary delivery by improving their dispersability, absorbability and respirability.

Claims 18-20, 29 and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (6,043,214) in view of International Ingredient Dictionary and Handbook.

Jensen et al, discussed above, lacks specific disclosure on the inclusion of carboxylic acid in the formulation. However Jensen teaches that hydrochloric acid is added to the formulations to adjust the pH. On the other hand, International Ingredient Dictionary and Handbook discloses that carboxylic acids such as citric acids are well known pH adjusters in pharmaceutical and cosmetic formulations. Therefore, one of ordinary skill in the art would have been motivated to replace hydrochloric acid of Jensen with citric acid to perform a pH adjusting function. The expected result would be a successful formulation for the pulmonary delivery of insulin.

(11) Response to Argument

Applicant argues that "Jensen states that the invention disclosed therein is directed towards a method of producing a therapeutic powder formulation by a process involving precipitation of an aqueous solution comprising insulin and an absorption enhancer to produce a powder formulation". Applicant continues to argue that "Jensen's disclosure of a process for preparing a formulation by precipitation teaches away from presently claimed invention". This is not persuasive. Jensen teaches that precipitation results in a "better" stability profile than powders of essentially the same composition prepared by spray drying. A preferred embodiment is not teaching away from the broadest disclosure. It is clear from Jensen's statement that spray drying the insulin

formulation has been done and has produced powders with some stability. Thus this not considered teaching away.

Applicant states that "Jensen himself teaches that the products possess the properties described therein because of the process used to produce the products". This is not persuasive. The properties Applicant is referring to are stability and absorption enhancement, properties that are not an issue in the instant claims. Applicant states that Jensen is producing insulin particles by precipitation, whereas spray drying method allows control over the particle size and density. This is not persuasive because 1) As far as the particle size is concerned it is believed that those are achieved by other methods such as milling. 2) specification does not teach that spray drying method is providing control over size and density of the particles. Furthermore, as mentioned in the previous Office Action, the instant claims are drawn to a method of delivery and not a method of making particles, thus the specific steps of preparation are not examined here and not given patentable weight. The method of delivery requires delivering particles of an active agent such as insulin complexed with a metal cation such as zinc to the pulmonary system, where the particles have a specific size and density limitation. Jensen is teaching delivering particles of insulin-zinc to the pulmonary system. The particles have a diameter of between 1 and 5 micron. Maa teaches delivery of insulin particles to the pulmonary system, where the particles have a diameter of 1 to 5 micron and a tap density of less than 0.4 g/cm^3. Additionally Maa et al teach that protein powders such as insulin are spray dried. Thus it has successfully

been shown that the combination of Jensen and Maa et al provide sufficient teachings for one of ordinary skill in the art to make and use the invention as claimed.

Applicant argues that Jensen produces crystals and Weers discloses hollow particles. These arguments are not commensurate with the scope of claims because the instant claims do not exclude crystals or hollow particles.

Applicant believes that Jensen and Maa references can not properly be combined because Jensen teaches away from Maa. This is not persuasive. As mentioned above, Jensen is **not** teaching away from Maa, but rather chooses precipitation as their preferred method. Furthermore, both Maa and Weers teach spray drying of insulin particles and their particles have the size and density limitation of the instant claims. What is missing from these two references is adding the metal cation such as zinc to active agent particles. Jensen is teaching that zinc and protamine are complexed with insulin and are available in the market (see col. 1, lines 32-37). Thus the combination of Jensen and Maa or Jensen and Weers are meeting all the limitations of the instant claims.

Applicant believes that combination of Jensen, Weers and the International Ingredient Dictionary and Handbook is in not proper because the Hand book "does not provide what the Jensen and Weers references lack". This is not persuasive because what the Jensen and Weers references lack is using carboxylic acid in the formulation. Handbook teaches that citric acids are well known pH adjusters and buffers, thus one of ordinary skill in the art would be motivated to refer to an Ingredient Dictionay and Handbook to find suitable ingredients for a formulation and also it would be obvious to

substitute a good pH adjuster and buffering agent for another pH adjuster (citric acid has two functions, thus being a preferred agent).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Mina Haghighatian
May 12, 2005

Conferees
Gary Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Sreeni Padmanbhan

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

ELMORE CRAIG, P.C.
209 MAIN STREET
N. CHELMSFORD, MA 01863